REMARKS

Status of the Claims

Claims 1, 3 and 7 are pending. Claims 1, 3 and 7 are rejected. Claim 1 is amended herein. Claims 2, 4-6 and 8-22 are canceled. No new matter has been added.

Refund

The Examiner stated that the fee Applicants paid for a Notice of Appeal, filed November 6, 2003, either may be refunded or may be credited for a future appeal. Applicants hereby request that the $640 ($165 fee to file the Notice of Appeal under 37 C.F.R. 1.17(b) and the $475 fee for a Petition for a Three Month Extension of Time under 37 C.F.R. 1.17(a)(3)) be refunded as a credit to Deposit Account No. 07-1185 upon which the undersigned Counsel is allowed to draw.

Claim amendments

Claim 1 has been amended to overcome 35 U.S.C. 112, first and second paragraphs, rejections as discussed *infra*. Claim 1

is amended to replace the word "systemically with the word "intravenously" as the means of administering the high specific activity construct. Claim 1 also is amended to correct grammar. No new matter is added.

The 35 U.S.C. §112, first paragraph, rejection

Claims 1, 3 and 7 are rejected under 35 U.S.C 112, first paragraph, as the specification does not contain a written description of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner states that the limitation of a method for killing a solid tumor larger than 1 mm in diameter, comprising "systemically" administering a dose of high specific activity Bi-213-antibody construct has no clear support in the specification and the claims as originally filed. The Examiner states that "systemically" administering the dose broadens the scope of the invention as originally disclosed in the specification.

Applicants have amended claim 1 to recite "intravenously" administering the dose of high specific activity construct to a human. It is standard in the art to administer a

therapeutic radiolabeled composition to an individual intravenously. The specification discloses that patients receive escalating doses of Bi-213-HuM195 via IV push (pg. 57, ll. 19-21).

Although Applicants have amended claim 1 to delete the term "systemically", Applicants respectfully submit that it is well-known in the art that "systemically" is synonymous with "intravenously" in the context that an intravenously administered composition is administered directly to the systemic circulation. Also, Applicants respectfully submit that "systemically" and "intravenously" are qualifiers that limit the original step of administering the construct and cannot broaden the scope of the claims over the generic recitation of "administering".

Accordingly, in view of the claim amendment and arguments presented herein, Applicants respectfully request that the rejection of claims 1, 3 and 7 under 35 U.S.C., 112, first paragraph, as containing new matter be withdrawn.

The 35 U.S.C. §112, first paragraph, rejection

Claims 1, 3 and 7 are rejected under 35 U.S.C 112, first paragraph, as containing subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner states that the while the specification is enabling for a method of killing a solid tumor larger than 1 mm in diameter by administering to a tumor a dose of high specific activity of Bi-213-antibody construct to the tumor repeatedly (pg. 8, ll. 4-6; pgs. 43-46, Ex. 12-13), it does not reasonably provide enablement for "systemically" administering the Bi-213 construct. The Examiner also states the specification discloses that different from Ac-225, Bi-213 has a short half life of 46 minutes and targeting must be rapid (pg. 22, Table 2). The Examiner cites **Maloney** *et al.* (Blood, 84(8):2457-66) as teaching the serum half-life for an antibody is about 4.4 days.

Furthermore, the Examiner states that one cannot extrapolate the teaching in the specification to the scope of the claims. The Examiner states that **Simonson** *et al.*, of record, teaches that a large solid peritoneal cancer could be effectively treated by Bi-212-antibody conjugate administered intraperitoneally (pg. 985s, first col., last PP) and it is unpredictable that Bi-213-

labeled antibody, when administered systemically, could reach the large tumor, because of the short half-life of Bi-212 or Bi-213. Thus, the Examiner concludes that in view of the absence of objective evidence and in view of the teaching of the art, one cannot predict that Bi-213 antibody conjugate, when administered systemically, could reach the large solid tumor, which could be anywhere in the body, in sufficient time to have sufficient radioactivity for killing the large tumor before the radioactivity is mostly decayed. It would therefore require undue experimentation for one of skill in the art to practice the claimed invention.

As discussed *supra*, Applicants have amended independent claim 1 to recite the term "intravenously" administering the construct which is the standard practice in the art for patient radiotherapy and taught in the instant specification. Applicants reiterate previous arguments and state that the method, as recited in amended claim 1, requires that the high specific activity of any alpha emittor used in the practice of the invention be within the range of 0.1 mCi/mg to about 30 mCi/mg and be sufficient for a pharmacologically effective dose of the construct to provide an amount of antibody to bind to a plurality of targeted

sites on the tumor cells such that a minimum of one atom of the alpha particle-emitting isotope delivers at least one alpha track to the tumor cells upon binding.

The specification teaches that designing a high specific activity antibody construct appropriate for the specific alpha emittor and targeted tumor cell takes into consideration the half-life of the isotope, the number of binding sites for the antibody on the target cell, the stability of the conjugate at the site upon targeting, the affinity of the conjugate for the target, the length of time required to deliver the conjugate and the total number of target sites or nonspecific binding sites in the patient. This information is accessible or is within the skill of one in the art to determine without undue experimentation.

Thus, a high specific activity antibody construct may be designed that will target and deliver at least one alpha to a tumor cell even if the alpha emitting isotope has a short half-life, such as 46 min for Bi-213 or 60 minutes for Bi-212. The specification provides an example for calculating a minimum specific activity for Bi-213 or Bi-212 for a cell with 10,000 binding sites of about 10 mCi/mg and extrapolates to other numbers of binding sites (pg. 15,

ll. 13 to pg. 17, ll. 5). In considering Bi-213, the specification teaches that the radiobismuth-labeled antibody demonstrates a greater tumoricidal effect if the Bi-213 is internalized (pg. 49, ll. 4-6). The specification also teaches that a Bi-213 isotope with high specific activity demonstrated approximately 50% killing when 2.0-2.5 atoms were initially bound onto the target cell surface having about 1-4 x 10^4 binding sites, such as LnCaP prostate tumor cells, where the average internalization time is 60 minutes (pg. 49, ll. 7-20).

The Examiner cited **Maloney** *et al.* as teaching that the median serum half-live of an antibody is 4.4 days. This refers to the persistence of circulating antibodies in the blood before removal by catabolic processes. The antibodies comprising the instant claimed radiolabeled constructs target solid cancers rather than disseminated cancers. Any intravenously administered construct will be delivered to the tumor vasculature within minutes. The time required to internalize the Bi-213-labeled antibody would depend upon the targeted antibody, but would range up to several hours. However, this is taken into consideration when determining the specific activity of the construct, as discussed herein. Furthermore,

as discussed *infra*, the specification demonstrates that a high specific Bi-213 antibody construct can target a solid tumor and subsequently kill the tumor.

The teachings in **Simonson** *et al.* and other prior art disclosures notwithstanding, the instant specification specifically teaches that solid tumors can be killed by short-lived alpha emitting conjugated ligands. Regarding the Examiner's statement about the lack of objective evidence, the specification provides specific in vivo examples that a Bi-213 antibody construct is effective against a solid tumor. Treating a 5 mm macroscopic prostate tumor *in vivo* with one dose of Bi-213 labeled J591 antibody specific for prostate cancer cells demonstrated a significant decrease in the rate of increase of measurable serum PSA in comparison to control (pg. 43, ll. 4-16; pg. 44, ll. 12 to pg. 46, ll. 16). Additionally, the specification teaches that Bi-213 labeled radioactive J591 prostate specific antibody administered to nude mice slowed the growth of a macroscopic LnCaP tumor (pg. 43, ll. 17 to pg. 44, ll. 3).

Thus, even with a 46 minute half life, a high specific activity Bi-213 antibody construct can be intravenously administered, delivered to the solid tumor vasculature, extravasate

the vasculature, target the tumor cell, and be internalized so that the Bi-213 can at least effect tumor growth. The specification also teaches that repeated administration will kill a solid tumor (pg. 48, ll. 1-12; Fig. 2). Furthermore, since time is a constraint when using a radioisotope with a short half-life, the specification teaches that Bi-213 and the antibody construct can be prepared onsite from a generator (pg. 27, ll. 1 to pg. 32, ll. 21). This generator is taught in Applicants' U.S. Patent No. 6,603,127.

Applicants reiterate that the claims do not recite a method where Bi-213 having any specific activity within the claimed range would kill any large tumor greater than 1 mm in diameter. It is a key element of the claims that the specific activity must be high enough to deliver at least one alpha to at least one cell. The specification teaches how to do this. Therefore, one of ordinary skill in the art can certainly make and intravenously administer an appropriately high specific activity Bi-213 antibody construct with the reasonable expectation that it will kill any tumor cell into which it is internalized without undue experimentation. Accordingly, in view of the claim amendment and arguments presented herein,

Applicants respectfully request that the rejection of claims 1, 3 and 7 under 35 U.S.C., 112, first paragraph, scope be withdrawn.

Applicants submit that claims 1, 3 and 7 are in condition for allowance. Accordingly, Applicants request that claims 1, 3 and 7 be passed to issuance. This is intended to be a complete response to the Office Action mailed May 18, 2004. If any issues remain, the Examiner is respectfully requested to telephone the undersigned attorney for immediate resolution. Applicants believe that no fees are due, however, should this be in error, please debit Deposit Account No. 07-1185 on which the undersigned is allowed to draw.

Respectfully submitted,

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